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with alkylating agent chemotherapy.

In summary, second cancers and leukemia account for only a fraction of cancer deaths, and their incidence is small compared to the benefits of radiation therapy.

—Alison Grann, MD
—Beryl McCormick, MD

References

1. Cahan WG, Woodard HQ, Higinbotham NL, et al: Sarcoma arising in irradiated bone: Report of eleven cases. 1948 . *Cancer* 82:8-34, 1998.

2. Phillips KA, Glendon G, Knight JA: Putting the risk of breast cancer in perspective. *N Engl J Med* 340:141-144, 1999.

3. Fisher B, Anderson S, Redmond CK, et al: Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 333:1456-1461, 1995.

4. Veronesi U, Luini A, Del Vecchio M, et al: Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 328:1587-1591, 1993.

5. Lichter AS, Lippman ME, Danforth DN, Jr, et al: Mastectomy vs breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: A randomized trial at the National Cancer Institute. *J Clin Oncol* 10:976-983, 1992.

6. Overgaard M, Hansen PS, Overgaard J, et al: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 337:949-955, 1997.

7. Fortin A, Larochelle M, Laverdiere J, et al: Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. *J Clin Oncol* 17:101-109, 1999.

8. Ragaz J, Jackson SM, Le N, et al: Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 337:956-962, 1997.

9. Fisher B, Dignam J, Wolmark N, et al: Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol* 16:441-452, 1998.

10. Wolmark N, Dignam J, Fisher B: The addition of tamoxifen to lumpectomy and radiotherapy in the treatment of ductal carcinoma in situ (DCIS): Preliminary results of NSABP Protocol B-24 (abstract). *Breast Cancer Res Treat* 50:1, 1998.

The Neugut et al Article Reviewed

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Major changes in the treatment of early-stage breast cancer began in the mid-1980s, following publication of the results of clinical trials indicating little or no difference in survival between women treated with breast-conserving surgery and whole-breast irradiation and those treated with mastectomy.[1] This finding, together with improvements in the early detection of breast cancer, resulted in substantial increases in the use of the more conservative procedures and in the number of young women who receive radiotherapy to the breast.

Today, the survival rate of patients with early-stage breast cancer is relatively high,[2] and large numbers of women live long enough to experience the late effects of treatment, including radiation-induced second cancers. Neugut and colleagues consider the possible magnitude of these risks.

Such an assessment is constrained by the long latency period of radiation-induced solid cancers, which typically are not diagnosed until at least 10 years following irradiation. As yet, no data have been published concerning the long-term risks of second cancers among large series of breast cancer patients treated with breast-conserving surgery and breast irradiation.

The largest, most detailed epidemiologic studies of second cancers among breast cancer patients were conducted in women diagnosed before 1986, at which time treatment often included mastectomy, with or without high-dose radiotherapy (orthovoltage or megavoltage) to the regional lymph nodes and chest wall. The nature of the radiation exposure before the middle 1980s was very different from that associated with contemporary practice. Neugut et al suggest, reasonably, that without direct evidence of the long-term effects of the more modern treatments, one can make reasonable predictions about second cancer risks based on the existing literature and a consideration of how the new treatments differ from the older techniques.

As always, such risks should be considered in the context of the mortality risks associated with the first breast cancer, the life-prolonging benefits of therapy, and the other possible complications of treatment besides second cancers. Among patients with localized breast cancer diagnosed between 1983 and 1987, the 5-year relative survival rate was 93.8% in whites and 84.1% in blacks.[2] Radiotherapy administered following breast-conserving surgery has been shown to result in a threefold lower rate of local tumor recurrence, compared with surgery alone, and to decrease mortality due to breast cancer.[3,4]

Second Cancers Potentially Increased by Breast Irradiation

Second cancers that have been reported to be increased among women irradiated for breast cancer include leukemia (except chronic lymphocytic leukemia) and cancers of the breast, lung, bone, soft tissue, and, possibly, esophagus. Of these, cancers of the lung and breast pose the greatest potential concern because of their high background incidence rates and demonstrated susceptibility to induction by radiation in other populations. Even a small relative increase in the risk of these cancers due to radiotherapy could translate into a substantial excess absolute risk. In contrast, leukemia, bone and soft-tissue sarcomas, and esophageal cancer would remain rare even if their incidences were increased two- or threefold by radiation therapy.

Radiotherapy administered after breast-conserving surgery can follow

any of a number of treatment plans, depending on which nodal volumes are to be irradiated, and incidental doses to healthy tissues vary accordingly.[5,6] In general, however, the use of tangential fields delivers lower doses to the contralateral breast, lungs, bone, bone marrow, and esophagus compared to the doses associated with adjuvant, high-dose regional radiotherapy to the nodes and chest wall following mastectomy.[6] Second cancer risks for these sites due to breast irradiation probably are lower, possibly substantially, than the risks associated with regional radiotherapy; thus, the latter estimates provide the likely upper bounds of the risks associated with more modern treatments.

Studies of secondary breast cancer, lung cancer, and leukemia among women diagnosed with breast cancer before 1986 all indicate a low overall absolute risk associated with radiotherapy. However, in each case, there is evidence of the modification of the effects of radiotherapy by other factors. Important effect modifiers include: age at irradiation for secondary breast cancer, smoking behavior for secondary lung cancer, and chemotherapeutic agents for leukemia.

Age at Irradiation and Secondary Breast Cancer

Boice and colleagues showed that, among all women with a first breast cancer, the risk of cancer of the contralateral breast was not significantly associated with radiotherapy; these investigators estimated that fewer than 3% of second breast cancers could be attributed to radiotherapy.[7] However, the relative risk of a second breast cancer was inversely associated with age at treatment and increased significantly with radiation dose among women younger than 45 years at diagnosis of the first breast cancer. The estimated relative risk was 2.26 for women younger than 35 years at diagnosis. No excess risk was apparent until 10 or more years following treatment.

Breast cancer is rare before the age of 35 years, and the general conclusion that the overall risk of contralateral breast cancer due to radiotherapy is low seems secure.[7,8] Nonetheless, further evaluation of the risk of radiation-induced secondary breast cancer among women whose first breast cancer was diagnosed at a young age is indicated, particularly in light of the trend toward earlier diagnosis of breast cancer and the very high relative risks observed during adolescence and early adulthood following mantle irradiation for Hodgkin's disease.[9] Also, special care should be taken to minimize the scatter dose to the contralateral breast in women younger than 45 years. Techniques for accomplishing this have been described.[5,10]

The risk of radiation-induced second breast cancer has led some to question the use of breast-conserving surgery and adjuvant radiotherapy in women with very-early-onset breast cancer.[9] Clinicians should take into account the fact that the scatter dose to the contralateral breast associated with breast-conserving therapy[10] typically is substantially lower than the doses associated with regional or mantle radiation in previous studies of patients with breast cancer or Hodgkin's disease. Women diagnosed with a first breast cancer should be followed closely to detect tumor recurrences and second primary breast cancers, but this is true whether or not they were irradiated.

Smoking and Secondary Lung Cancer

High-dose, regional radiotherapy following mastectomy is associated with an approximately twofold relative risk of lung cancer among 10-year survivors of breast cancer.[11] The absolute risk attributable to radiotherapy has been estimated at 9 excess cases per year among 10,000 women who survived for at least 10 years.

The risk associated with thoracic irradiation appears to be considerably greater among smokers than among nonsmokers.[12,13] In patients with Hodgkin's disease, the combined effect of radiotherapy and continued smoking appeared to be more than multiplicative.[13] Minimization of future lung cancer risk among newly diagnosed breast cancer patients who smoke calls for modification of their smoking behavior rather than their breast cancer treatment.

Chemotherapeutic Agents and Secondary Leukemia

Unlike radiotherapy-induced breast and lung cancers, which generally have long latency periods and then remain in excess over an extended period, radiogenic leukemia begins to appear within several years following treatment and demonstrates a wavelike excess in relative risk over time. The most detailed study of treatment-induced leukemia among breast cancer patients indicates a possible multiplicative relationship between the risks due to radiotherapy and chemotherapy.[14] Investigators observed a 2.4-fold relative risk associated with high-dose regional radiotherapy in the absence of chemotherapy, a 10-fold relative risk due to chemotherapy with alkylating agents in the absence of radiotherapy, and a 17.4-fold relative risk associated with combined radiotherapy and chemotherapy. The excess risk was concentrated within the first 7 years following treatment.

The risk associated with chemotherapy was especially high for melphalan (Alkeran) and substantially lower for cyclophosphamide (Cytoxan, Neosar). The high relative risk associated with combined-modality therapy probably is not representative of the risks associated with contemporary treatments, insofar as melphalan and high-dose regional radiotherapy are rarely used today, and cyclophosphamide is given for shorter periods.

Summary

In summary, important scientific questions remain concerning the joint effects of radiotherapy and other carcinogenic exposures, and the possible existence of subgroups of patients at elevated risk for second cancers. Nevertheless, the overall risk of radiotherapy-induced second cancers associated with current treatments for breast cancer appears to be small and not of overriding importance from the standpoint of management of the first breast cancer. This conclusion is supported by the low and delayed excess risk observed in studies of women who received high-dose regional radiotherapy for breast cancer, and the generally lower radiation doses to healthy tissues outside of the breast that are associated with breast-conserving therapy.

The issue of second cancers after breast irradiation must be revisited periodically, as it is possible that new drugs will interact with radiotherapy to produce high risks, or that small subgroups with dramatically heightened suscepti-

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bility will be identified. It always is desirable to avoid unnecessary exposure of healthy tissue to ionizing radiation. However, this principle already is incorporated into the practice of radiation oncology and must be balanced against the goals of enhancing local tumor control and, ultimately, increasing survival. Finally, other possible adverse consequences of radiotherapy following breast-conserving surgery, including an unsatisfactory cosmetic outcome in the affected breast, may be more important considerations for many patients.

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References

1. Harris JR, Recht A, Connolly J, et al: Conservative surgery and radiotherapy for early breast cancer. *Cancer* 66:1427-1438, 1990.
2. Miller BA, Ries LAG, Hankey BF, et al: *SEER Cancer Statistics Review: 1973-1990.* NIH publication no. 93-2789. Bethesda, Maryland, National Cancer Institute, 1993.
3. Early Breast Cancer Trialists' Collaborative Group: Effects of radiotherapy and surgery in early breast cancer: An overview of randomized trials. *N Engl J Med* 333:1444-1455, 1995.
4. Fisher B, Anderson S, Redmond CK, et al: Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 333:1456-1461, 1995.
5. Lichter AS, Fraass BA, Yanke B: Treatment techniques in the conservative management of breast cancer. *Semin Oncol* 2:94-106, 1992.
6. Perez CA, Taylor ME: Breast: Stage Tis, T1, and T2 tumors, in Perez CA, Brady LW (eds): *Principles and Practice of Radiation Oncology*, 3rd ed, pp 1269-1414. Philadelphia, Lippincott-Raven, 1997.
7. Boice JD Jr, Harvey E, Blettner M, et al: Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med* 326:781-785, 1992.
8. Storm HH, Andersson M, Boice JD Jr, et al: Adjuvant radiotherapy and risk of contralateral breast cancer. *J Natl Cancer Inst* 84:1245-1250, 1992.
9. Hancock SL, Tucker MA, Hoppe RT: Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 85:25-31, 1993.
10. Fraass BA, Roberson PL, Lichter AS: Dose to the contralateral breast due to primary breast irradiation. *Int J Radiat Oncol Biol Phys* 11:485-497, 1985.
11. Inskip PD, Stovall M, Flannery JT: Lung cancer risk and radiation dose among women treated for breast cancer. *J Natl Cancer Inst* 86:983-988, 1994.
12. Neugut AI, Murray T, Santos J, et al: Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers. *Cancer* 73:1615-1620, 1994.
13. van Leeuwen FE, Klokman WJ, Stovall M, et al: Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. *J Natl Cancer Inst* 87:1530-1537, 1995.
14. Curtis RE, Boice JD Jr, Stovall M, et al: Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N Engl J Med* 326:1745-1751, 1992.